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U1S S2410

(56) Documents Cited:
EP 1227102 A1 **WO 1989/000576 A1**

(58) Field of Search:
Other: **Online:WPI,EPODOC,JAPIO,CAS ONLINE**

(54) Abstract Title: **Process for preparing non-hygroscopic azithromycin dihydrate**

(57) A direct, single step process for preparing a semi-synthetic antibiotic azithromycin dihydrate (non-hygroscopic) is provided, by in situ reductive N-methylation of azaerythromycin A and subsequent crystallization from a mixture of acetone and water, preferably together with a catalytical quantity of a base such as liquor ammonia. The process comprises:

a) reacting azaerythromycin A with formic acid and formaldehyde in an organic solvent medium, to form a reaction mass comprising N-methylated azaerythromycin A (i.e. azithromycin);

b) adding aqueous alkali solution to the reaction mass to form an aqueous phase and an organic phase;

c) (i) when the organic solvent medium is acetone, separating the aqueous phase from the acetone organic phase, and removing the aqueous phase; or

(ii) when the organic solvent medium is a solvent other than acetone, separating the aqueous phase from the organic phase and removing the aqueous phase, optionally washing the separated organic phase with aqueous alkali solution, completely distilling off the solvent from the organic phase to leave a residue, and adding acetone to dissolve the residue and form an acetone organic phase;

d) adding water, and optionally a base, to the acetone organic phase to form a mixture, and allowing crystals to form in the mixture;

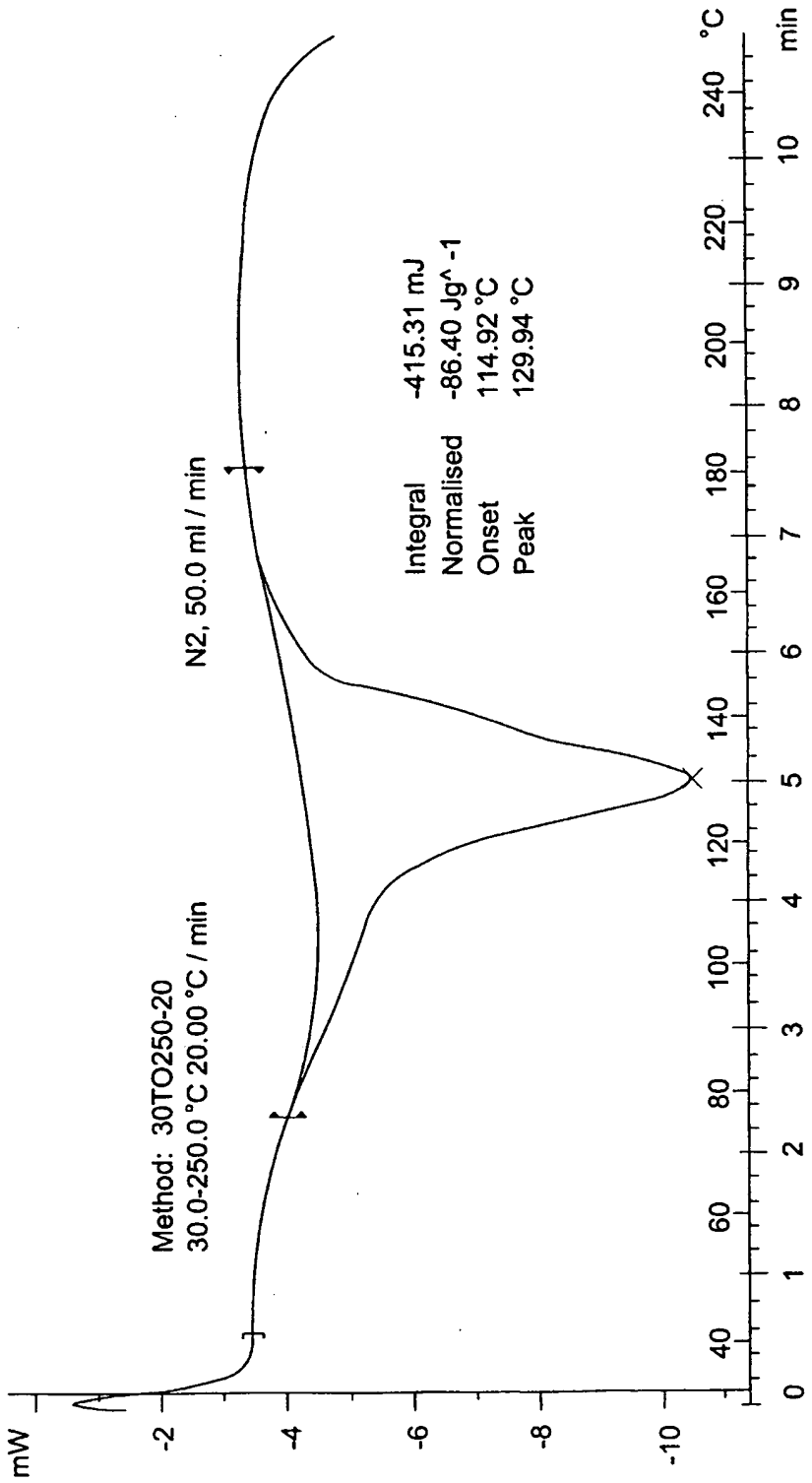
e) recovering the crystals from the mixture and optionally washing the crystals;

f) drying the crystals to obtain non-hygroscopic azithromycin dihydrate.

Non-hygroscopic azithromycin dihydrate of a pharmaceutically acceptable quality is obtainable in yields up to 78-82% w/w.

GB 2 395 482 A

At least one drawing originally filed was informal and the print reproduced here is taken from a later filed formal copy.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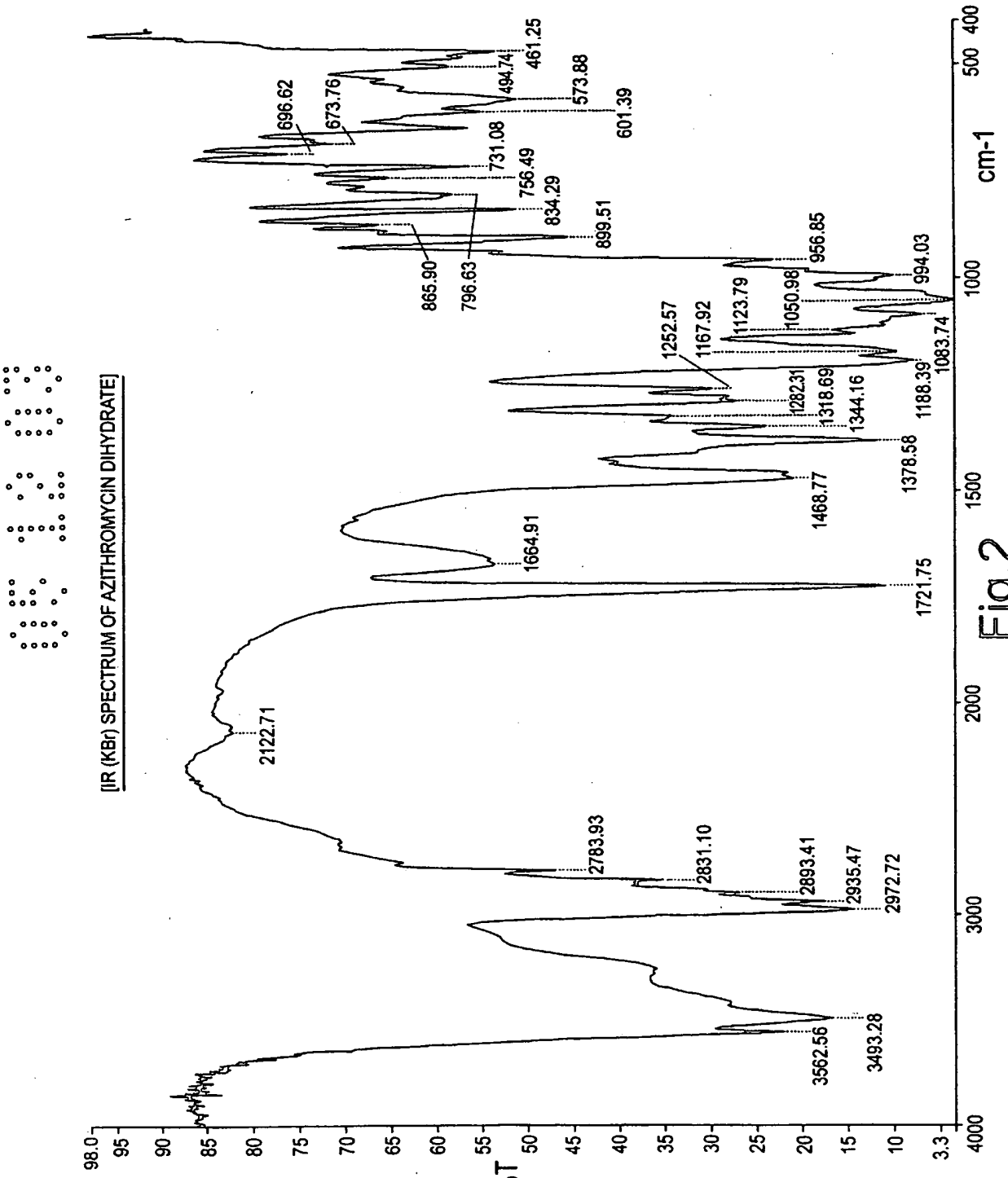
N2, 50.0 ml / min
Integral -415.31 mJ
Normalised -86.40 Jg^-1
Onset 114.92 °C
Peak 129.94 °C
mW
-2
-4
-6
-8
-10
40
60
80
100
120
140
160
180
200
220
240
°C
0
1
2
3
4
5
6
7
8
9
10
min

Fig.1


[IR (KBr) SPECTRUM OF AZITHROMYCIN DIHYDRATE]
%T
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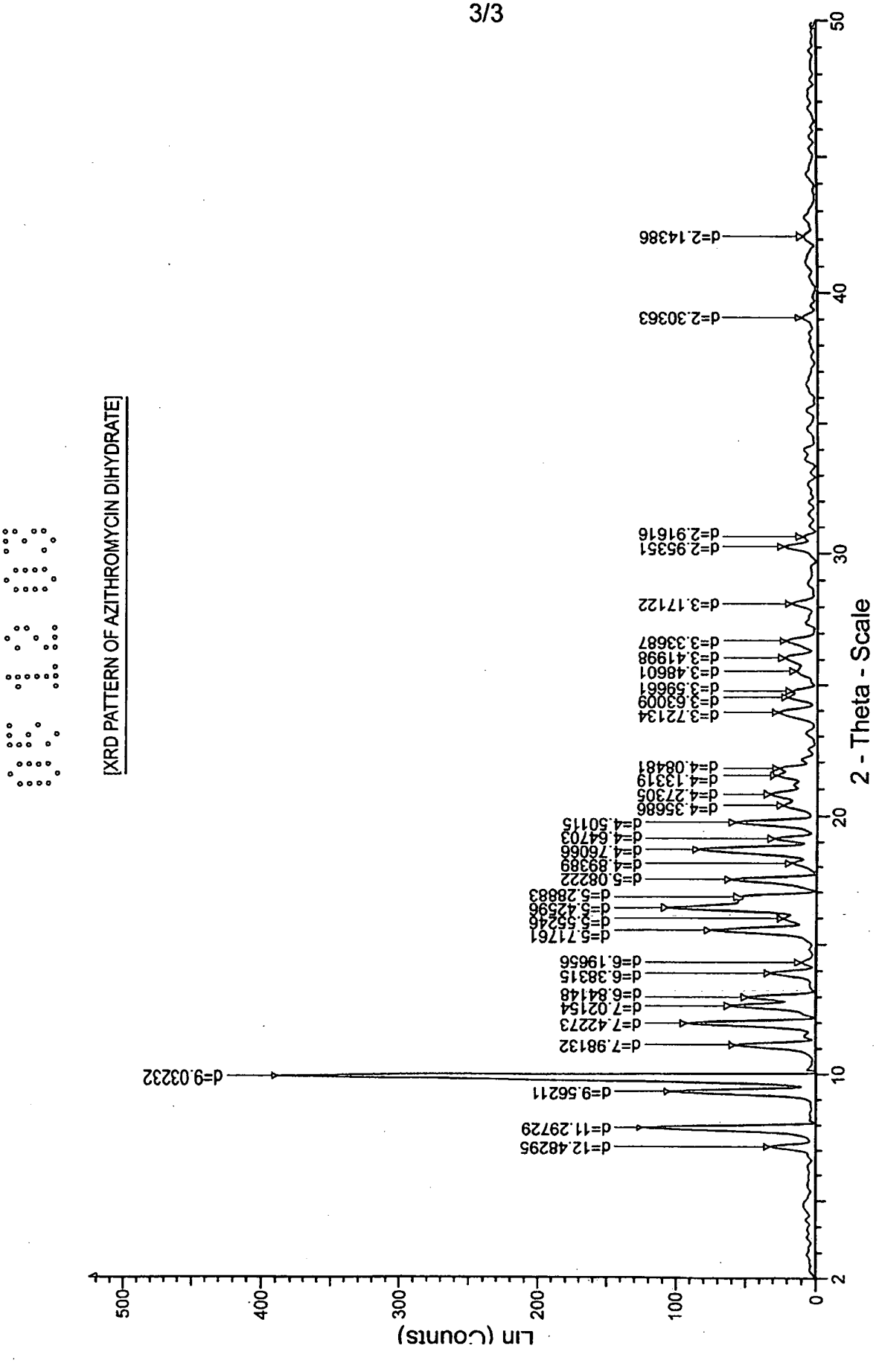
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
3.3
4000
3000
2000
1500
1000
500
400
3562.56
3493.28
2972.72
2935.47
2893.41
2831.10
2783.93
2122.71
1721.75
1664.91
1468.77
1378.58
1344.16
1318.69
1282.31
1252.57
1188.39
1167.92
1123.79
1083.74
1050.98
994.03
956.85
899.51
865.90
834.29
796.63
756.49
731.08
696.62
673.76
601.39
573.88
494.74
461.25

Fig.2


[XRD PATTERN OF AZITHROMYCIN DIHYDRATE]
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d=12.48295
d=7.98132
d=7.42273
d=7.02154
d=6.84148
d=6.38315
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d=5.71761
d=5.55246
d=5.42596
d=5.28883
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d=4.89389
d=4.76066
d=4.64703
d=4.50115
d=4.35686
d=4.27305
d=4.13319
d=4.08481
d=3.72134
d=3.63009
d=3.59661
d=3.48601
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d=3.33687
d=3.17122
d=2.95351
d=2.91616
d=2.30363
d=2.14386

Fig.3

Process for preparing non-hygroscopic azithromycin dihydrate

Background of the Invention

Field of the Invention:

This invention relates to a direct single step preparation of the semi-synthetic antibiotic azithromycin dihydrate (non-hygroscopic).

Description of the Prior Art:

9a-Aza-9a-methyl-9-deoxo-9a-homoerythromycin A, better known by its generic name azithromycin, is a broad spectrum semi-synthetic macrolide antibiotic compound belonging to the erythromycin A family, and processes for its preparation in the monohydrate form are disclosed in the US-A-4, 517,359 and US-A-4,474,768. However, the azithromycin monohydrate form thus prepared, also referred to as hygroscopic azithromycin monohydrate or azithromycin crude, is difficult to handle during formulation, due to its hygroscopic properties. The molecular structure of hygroscopic azithromycin monohydrate is shown by formula (II) in the Scheme below.

EP-A-0 298 650 describes the preparation of a new form of azithromycin, *viz* azithromycin dihydrate, which is essentially non-hygroscopic under the conditions of relative humidity conducive to the formulation of azithromycin. The molecular structure of non-hygroscopic azithromycin dihydrate is shown by formula (III) in the Scheme below. According to this reference, azithromycin dihydrate is prepared from hygroscopic azithromycin monohydrate which, in turn, is prepared from 9-deoxo-9a-aza-9a-homoerythromycin A, also known as azaerythromycin A, having the molecular structure shown by formula (I) in the Scheme below. Azaerythromycin A is subjected to a reductive N-methylation reaction using a solution of formic acid and formaldehyde in chloroform medium followed by stripping off of the solvent and precipitation from a mixture of ethanol and water, to furnish hygroscopic azithromycin monohydrate in a yield of 85% w/w from azaerythromycin A. The hygroscopic azithromycin monohydrate, as obtained above, is then crystallized from a mixture of tetrahydrofuran, hexane and 2-4 molar equivalents of water at a temperature varying from 17°C to 40°C to furnish azithromycin dihydrate in about 90% w/w yield from hygroscopic azithromycin monohydrate. The overall yield of azithromycin dihydrate is 76% w/w (71% of theoretical) from azaerythromycin A, in two steps.

However, drawbacks of the above process are that high volumes (20 times on azaerythromycin A input) of solvent mixtures are required for the crystallization, and that it is necessary to isolate the hygroscopic azithromycin monohydrate.

Several other prior art methods are known for preparing azithromycin dihydrate from azithromycin monohydrate or azithromycin crude. These methods use, for the crystallization, a mixture of acetone/water (EP-A-0 827 965 & US-A-20010047089);

a mixture of isopropyl alcohol/water, acetonitrile/water, dimethylformamide/water or dimethylacetamide/water (US-A-20020111318 A1); or a mixture of tert-butanol/water or tert-butanol/petroleum ether/water (EP-A-1 234 833). Azithromycin dihydrate may also be made by dissolving azithromycin monohydrate in water at acidic pH and raising the pH by adding aqueous NaOH to precipitate the dihydrate (WO-A-02/15842) or by using a mixture of acetone/water (EP-A-0 941 999).

WO-A-01/87912 discloses a process for preparing a new polymorph of azithromycin dihydrate, by crystallizing from azithromycin monohydrate in a mixture of acetone/water at 35-40°C. The melting point of this polymorph of azithromycin dihydrate is reported to be 139°C (DSC), whereas for azithromycin dihydrate the melting point reported previously according to EP-A-0 298 650 is 126°C-127°C (DSC).

A more recent publication WO-A-02/094843 discloses various new crystal forms of azithromycin that are essentially hydrates or hydrate-solvates of azithromycin free base, designated as C,D,E,F,G,H,I,J,K,L,M,N,O,P,Q,R. A dihydrate form A and a non-stoichiometric hydrate form B (hygroscopic monohydrate) have been disclosed previously in EP-A-0 298 650 and US-A-4,517,359 & US-A-4,474,768, respectively.

Therefore, it is evident from the above that prior art methods of preparing azithromycin dihydrate have, invariably, required at least two steps starting from azaerythromycin A. In the first step, azaerythromycin A is converted into either azithromycin crude or azithromycin monohydrate (hygroscopic), and in the second step the latter is crystallized into azithromycin dihydrate *e.g.* from solvent/solvent/water or solvent/water combinations or through acid/base treatment in water or in acetone/water mixtures.

Summary of the Invention

We have now found, surprisingly, that azithromycin dihydrate of a pharmaceutically acceptable quality can be prepared directly, in a single step, from azaerythromycin A, and in improved yields, without the need to isolate either the hygroscopic azithromycin monohydrate or the crude azithromycin.

Accordingly, the present invention provides a process for the preparation of non-hygroscopic azithromycin dihydrate directly from a reductive N-methylation reaction mass, comprising:

a) reacting azaerythromycin A with formic acid and formaldehyde in an organic solvent medium, to form a reaction mass comprising N-methylated azaerythromycin A (i.e. azithromycin);

b) adding aqueous alkali solution to the reaction mass to form an aqueous phase and an organic phase;

c) (i) when the organic solvent medium is acetone, separating the aqueous phase from the acetone organic phase, and removing the aqueous phase; or

(ii) when the organic solvent medium is a solvent other than acetone, separating the aqueous phase from the organic phase and removing the aqueous phase, optionally washing the separated organic phase with aqueous alkali solution, completely distilling off the solvent from the organic phase to leave a residue, and adding acetone to dissolve the residue and form an acetone organic phase;

d) adding water, and optionally a base, to the acetone organic phase to form a mixture, and allowing crystals to form in the mixture;

e) recovering the crystals from the mixture and optionally washing the crystals;

f) drying the crystals to obtain non-hygroscopic azithromycin dihydrate.

Brief Description of the Drawings

Figure 1 shows the differential scanning calorimetry (DSC) pattern of non-hygroscopic azithromycin dihydrate of formula (III) obtained in accordance with an embodiment of the invention;
Figure 2 shows the infrared (IR) absorption spectrum of the non-hygroscopic azithromycin dihydrate of formula (III);
Figure 3 shows the X-ray diffraction (XRD) pattern of the non-hygroscopic azithromycin dihydrate of formula (III).

Detailed Description of the Invention

According to the present invention, azaerythromycin A is subjected to a reductive N-methylation reaction using formic acid and formaldehyde in an organic solvent medium to form azithromycin.

The azaerythromycin A may be made by prior art procedures, for example as disclosed in J. Chem. Soc. (Perkin Trans) 1986, 1, p1881-1890.

The formic acid and formaldehyde are preferably added to the organic solvent medium as solutions, preferably as aqueous solutions, *e.g.* 80-90% aqueous formic acid solution and 30-37% aqueous formaldehyde solution, and may be added separately or together.

The organic solvent medium preferably is an organic solvent selected from chloroform, dichloromethane (methylene dichloride) and acetone, and more preferably is acetone.

The organic solvent is suitably present in a volume ratio of from 1 : 1 to 10 : 1, more preferably 2 : 1 to 5 : 1, with respective to the azaerythromycin A. If acetone is used as the organic solvent medium, the acetone should be present in a volume ratio of at least 2.5 : 1, and preferably is present in a volume ratio of from 2.5 : 1 to 4: 1, more preferably 3 : 1, with respective to the azaerythromycin A. The ratio of 3 : 1 is comfortable enough to facilitate smooth filtrations through polishing filters or activated carbon treatment, if necessary.

The reductive N-methylation reaction is carried out preferably at a temperature in the range from 25 to 60°C, more preferably at a temperature in the range from 38 to 55°C, for example 50 to 55°C.

When the reductive N-methylation reaction has been completed, the reaction mass is cooled or allowed to cool, preferably to room temperature or below. Once cooled, aqueous alkali solution is added to the reaction mass, which then forms an aqueous phase and an organic phase. Preferably, aqueous sodium hydroxide or aqueous potassium hydroxide, or a mixture thereof, is used. We prefer that the aqueous alkali solution is sodium hydroxide solution, more preferably 20-50% sodium hydroxide solution, and in particular 30% sodium hydroxide solution.

The aqueous layer is separated, and may be removed from the organic layer. The organic layer is preferably filtered, *e.g.* through a polishing filter, and is then heated to a temperature in the range from 25 to 40°C, preferably in the range from 38 to 40°C.

To initiate crystallization, water is then added gradually to the separated organic phase at a temperature in the range from 25 to 40°C, more preferably at a temperature in the range from 38 to 40°C. In addition, a base may be added, as described in more detail further below.

If the organic solvent medium is acetone, the water is added preferably in a volume ratio of from 1 : 1 to 2 : 1, more preferably in a volume ratio of 3 : 2, with respective to the acetone. If the ratio of water is more than 2 : 1 with respect to acetone, hygroscopic material is precipitated out whereas if the ratio of water is less than 1 : 1, the yield is decreased.

Preferably, the water is added gradually as two or three portions, preferably as two portions. The first portion of water may be added, preferably at 38-40°C, over a period of for example 30 minutes to 2 hrs, and preferably over a period of about 1 hour.

If acetone is used as the organic solvent, the first portion of water added is preferably in a volume ratio of 0.20 : 1 to 0.25 : 1, with respect to the acetone employed. If the first portion of water used is <0.2 : 1 of acetone, the crystallization is not sufficiently induced. However, if the first portion of water used is >0.25 : 1, premature precipitation takes place and furnishes a hygroscopic product.

After the addition of the first portion of water, the mixture is maintained to allow the formation of crystals. Preferably, the mixture is stirred during this time. The mixture is preferably maintained at the same temperature, for example for 1 to 5 hours, preferably for 1.5 to 4 hours, and more preferably for about 2 hours, to allow abundant formation of crystals. If desired, the mixture may optionally be seeded with azithromycin dihydrate.

The second portion of water is then added. If acetone is used as the organic solvent, the second portion is preferably in a volume ratio of 1.25 : 1 to 1.3 : 1, with respect to the acetone. The second portion of water is added, preferably at 38-40°C, over a period of for example 1 to 4 hours, in particular over a period of about 2 hours.

When all of the water has been added, the mixture is maintained at a temperature in the range from 25 to 40°C, more preferably at a temperature in the range from 30 to 40°C, and most preferably at a temperature in the range from 38 to 40°C. Higher temperatures *i.e.* more than 40°C may lead to degradation products, whereas temperatures lower than 25°C may speed up the formation of the product, resulting in hygroscopic material.

After addition of the second portion of water, the mixture is maintained at the temperature over a period of for example 6 to 12 hours, preferably 8 to 12 hours, more preferably 8 to 10 hours, for completion of crystallization process. Crystallisation cycle times of longer than 12 hours do not provide any advantages whereas times less than 6 hours may give lower yields. Preferably, the mixture is stirred during this time.

In a preferred embodiment, in addition to water, a base is added to the organic phase. The base may be added separately from or together with the water, and, if the water is added in two or more portions, is preferably added only after the first water portion has been added, *e.g.* together with only the second water portion. The base is preferably aqueous sodium hydroxide, aqueous potassium hydroxide or liquor ammonia (ammonium hydroxide), and most preferably is liquor ammonia. We have found that addition of a catalytic quantity a base such as liquor ammonia helps to improve the yield. The base may be added in such amount as to provide a pH in the range from 9.5 to 11, preferably 9.7 to 10.5, for the mixture. Typically, the quantity of liquor ammonia used is 0.1% w/v to 0.2% w/v with respect to azaerythromycin A input. The slightly enhanced yields obtainable when a base such as liquor ammonia is added may be due to the slight increase in the pH of the crystallization medium, *i.e.* to ~ 10.0 pH, effected by the base. In the absence of added base, the pH would be in the range of ~ 9.0 to 9.5. Since a more basic pH of the medium decreases the solubility of azithromycin, the yields are comparatively higher. However, an excessive amount of added base such as ammonia would produce a hygroscopic product.

When acetone is used as medium for the reductive N-methylation reaction, the same acetone medium is used for the crystallization as well. However, when employing other solvents, such as methylene dichloride or chloroform, for the reaction medium instead of acetone, the other solvent should be distilled off at the end of the N-methylation reaction, and the requisite quantity of acetone then added to the residue so as to form an acetone organic phase, before the crystallization process, as described above, is commenced (see experimental part for details). In this case, the acetone should be added in a volume ratio of at least 2.5 : 1, and preferably is present in a volume ratio of from 2.5 : 1 to 4: 1, more preferably 3 : 1, with respective to the initial azaerythromycin A input. The reaction medium is preferably washed with aqueous alkali, such as sodium hydroxide solution, before the solvent is distilled off.

Following the crystallization period, the mixture is preferably cooled or allowed to cool, e.g. to 10 to 15°C, and may be maintained at the cooling temperature for a period, for example for 1 to 3 hours. The crystals are then recovered, preferably by filtration, and are preferably washed, e.g. with water. Finally, the crystals are dried, preferably under vacuum, and preferably at a temperature in the range from 40 to 60°C, more preferably in the range from 45 to 50°C. The drying is preferably completed when the crystals attain a moisture content in the range from 4.5 to 5%.

In a preferred embodiment, acetone is used as the organic solvent medium, the reductive N-methylation reaction is carried out at 50-55°C, and, at the end of the reaction, the reaction mixture is stirred with a 30% aqueous solution of sodium hydroxide. The bottom aqueous layer is separated, and the top acetone layer, containing the product, is then filtered, e.g. through a polishing filter, and heated to 38-40°C. Water is then added in two portions, totalling to 1.5 v/v of the acetone, and the mixture is agitated for a period of 8-10hrs at 38-40°C. The crystallization slurry is then cooled to 10-15°C and separated by filtration. The wet product is washed with chilled water, unloaded and dried at 45-50°C until the moisture is constant (4.5 to 5%). The product i.e. azithromycin dihydrate, as made above, is stable and water content (KF) value is around 4.6 - 4.7%, with a melting point of 129-130°C (129.94°C by DSC, as shown in Figure 1) with characteristic infra-red (KBr) absorption values (as shown in Figure 2) and X-ray diffraction pattern (as shown in Figure 3).

EXAMPLES

The invention will be further illustrated by the following non-limiting examples:

EXAMPLE 1

100g (0.136g moles) of azaerythromycin A was dissolved in 300mL of acetone under stirring at room temperature. Formic acid (85%, 15.6g, 0.288g moles) and formaldehyde solution (37%, 14.10g, 0.1737g moles) were added and resulting

mixture was heated at 50 - 55°C for 8 hrs. The mixture was then cooled to room temperature and stirred with 16mL of 30% aqueous NaOH solution. The aqueous layer was separated and acetone layer containing material was filtered through polishing filter and the clear filtrate was heated to 38 to 40°C. The first portion of water (70mL) was added to this in about 1 hr maintaining a temperature of 38 to 40°C followed by stirring for 2hrs at the same temperature to allow abundant formation of crystals. The second portion of water (380mL) was then added in about 2 hrs and thereafter maintained for 8-10 hrs at 38-40°C. The resulting crystals were cooled to 10 to 15°C, maintained for 2hrs and recovered by filtration. The crystals were washed with 50mL X 2 of chilled water and dried under vacuum at 45 to 50°C till constant weight furnishing 80gms of azithromycin dihydrate in 80% w/w yield from azaerythromycin A (74.9% of theoretical) with a moisture content of 4.7%.

EXAMPLE 2

Example 1 was repeated except that the second portion of water used in the crystallization process contained 10mL of liq. ammonia (*i.e.* 370mL of water + 10mL of liq. ammonia). Thus, 82g of azithromycin dihydrate was obtained in 82% w/w yield from azaerythromycin A (76.7% of theoretical).

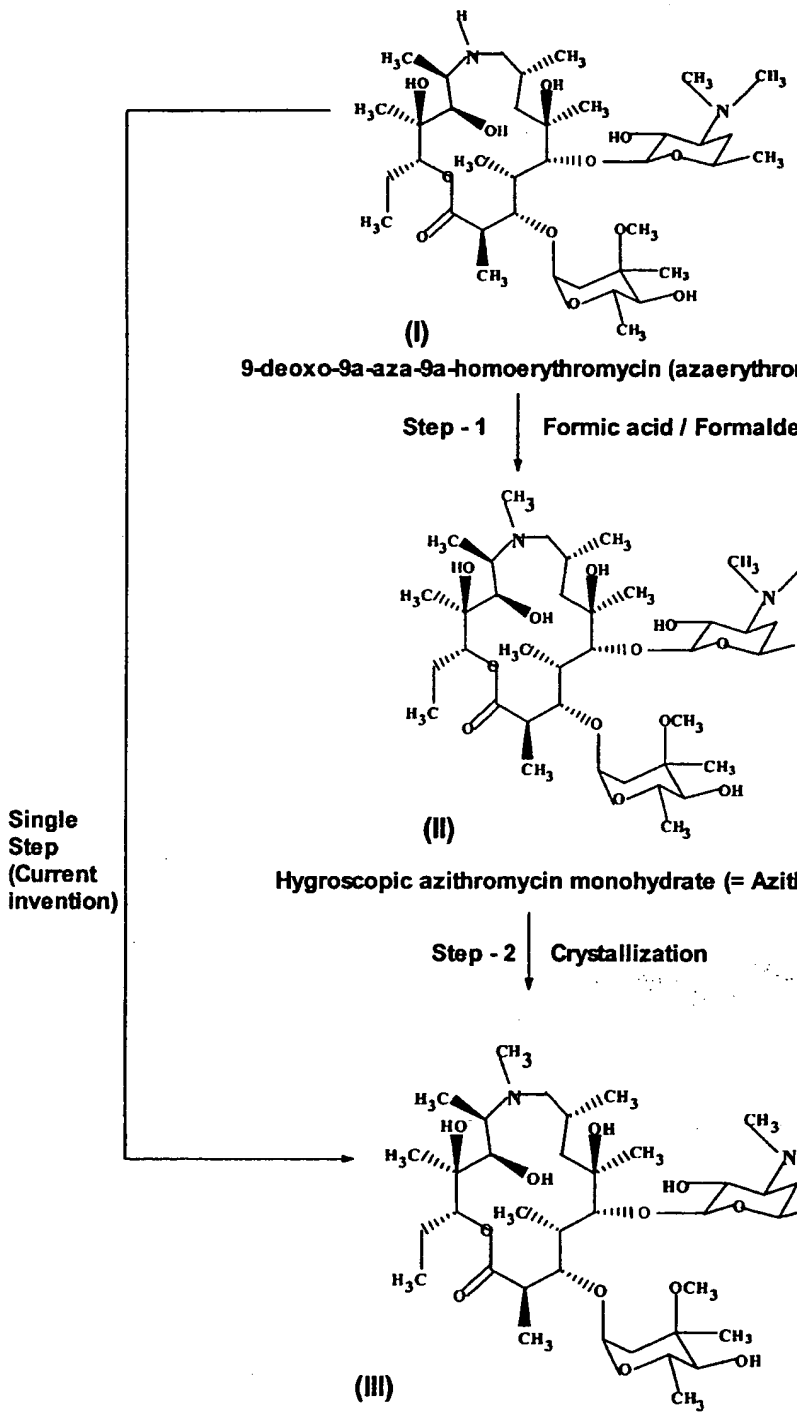
EXAMPLE 3

100g (0.136g moles) of azaerythromycin A was dissolved in 400mL of chloroform under stirring at room temperature. Formic acid (85%, 15.6g, 0.288g. moles) and formaldehyde solution (37%, 14.10g, 0.1737g moles) were added and the resulting mixture was heated at 50-55°C for 10hrs. The mixture was then cooled to room temperature and washed with 25mL X 2 of 10% aq. NaOH solution. The chloroform layer was separated, dried over anhydrous magnesium sulphate and distilled off completely under reduced pressure till dryness. This was further chased with 100mL of acetone till dryness. The residual product was cooled to room temperature and dissolved in 300mL of acetone and the resulting solution was filtered through polishing filter and crystallization was carried out as per the procedure given in Example 1 to get 78g of azithromycin dihydrate in 78% w/w from azaerythromycin A (73% of theoretical).

EXAMPLE 4

The procedure described in Example 3 was repeated but using methylene dichloride as a solvent during the reaction (20 hrs / reflux conditions) to furnish 80g of azithromycin dihydrate in 80% w/w yield from azaerythromycin A (74.9% of theoretical).

SCHEME


(I)
9-deoxo-9a-aza-9a-homoerythromycin (azaerythromycin A)
Step - 1
Formic acid / Formaldehyde
(II)
· H2O
Hygroscopic azithromycin monohydrate (= Azithromycin Crude)
Single Step (Current invention)
Step - 2
Crystallization
(III)
· 2H2O
Non-hygroscopic azithromycin dihydrate

CLAIMS:

1. A process for the preparation of non-hygroscopic azithromycin dihydrate directly from a reductive N-methylation reaction mass, comprising:

a) reacting azaerythromycin A with formic acid and formaldehyde in an organic solvent medium, to form a reaction mass comprising N-methylated azaerythromycin A (i.e. azithromycin);

b) adding aqueous alkali solution to the reaction mass to form an aqueous phase and an organic phase;

c) (i) when the organic solvent medium is acetone, separating the aqueous phase from the acetone organic phase, and removing the aqueous phase; or

(ii) when the organic solvent medium is a solvent other than acetone, separating the aqueous phase from the organic phase and removing the aqueous phase, washing the separated organic phase with aqueous alkali solution, completely distilling off the solvent from the organic phase to leave a residue, and adding acetone to dissolve the residue and form an acetone organic phase;

d) adding water, and optionally a base, to the acetone organic phase to form a mixture, and allowing crystals to form in the mixture;

e) recovering the crystals from the mixture and optionally washing the crystals;

f) drying the crystals to obtain non-hygroscopic azithromycin dihydrate.

2. A process according to claim 1, wherein the organic solvent medium is an organic solvent selected from chloroform, dichloromethane and acetone.

3. A process according to claim 2, wherein the organic solvent medium is acetone.

4. A process according to claim 3, wherein the acetone is present in a volume ratio of 3 : 1 with respective to the azaerythromycin A.

5. A process according to claim 1, wherein the reductive N-methylation reaction (a) is carried out at a temperature in the range from 25 to 60°C.

6. A process according to claim 5, wherein the reductive N-methylation reaction (a) is carried out at a temperature in the range from 50 to 55°C.

7. A process according to claim 1, wherein the aqueous alkali solution is an aqueous solution of sodium hydroxide or potassium hydroxide, or a mixture thereof.

8. A process according to claim 7, wherein the aqueous alkali solution is 30% sodium hydroxide solution.

9. A process according to claim 1, wherein the water is added gradually to the separated organic phase at a temperature in the range from 25 to 40°C.

10. A process according to claim 9, wherein the water is added gradually to the separated organic phase at a temperature in the range from 38 to 40°C.

11. A process according to claim 1, wherein the water is added as a first portion and a second portion.

12. A process according to claim 1, wherein the organic solvent medium is acetone and the water is added in a volume ratio of 3 : 2 with respective to the acetone.

13. A process according to claim 1, wherein a base is added to the separated organic phase, said base being selected from aqueous sodium hydroxide, aqueous potassium hydroxide and liquor ammonia.

14. A process according to claim 13, wherein liquor ammonia is added as the base in an amount to provide a pH in the range from 9.5 to 10 for the mixture.

15. A process according to claim 1, wherein the crystals are dried at a temperature in the range from 45 to 50°C to provide a moisture content in the range from 4.5 to 5%.

Application No:	GB 0315606.4	**Examiner:**	Peter Davey
Claims searched:	1-15	**Date of search:**	27 October 2003

Patents Act 1977 : Search Report under Section 17

Documents considered to be relevant:

Category	Relevant to claims	Identity of document and passage or figure of particular relevance	
A		EP 122710 A1	(ALEMBIC). see eg. claim 1 and Exs.
A		WO 89/00576 A1	(PFIZER), see eg. Ex. 1 and Prep. 1

Categories:

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

Field of Search:

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC[V]:

Worldwide search of patent documents classified in the following areas of the IPC[7]:

The following online and other databases have been used in the preparation of this search report:

WPI, EPODOC, JAPIO, CAS ONLINE